37-39, and withdrew claims 31-36 from consideration as being drawn to a nonelected invention. Claims 30-36 were cancelled in a response filed on January 17, 1995. Thus, claims 27, 29 and 37-39 are pending.

In an Advisory Action dated February 9, 1995, the Examiner stated that the term "extraneous protein" is unclear. During an interview with the Examiner on May 25, 1995, applicants' representatives stated that these claims would be amended to delete the term, and the Examiner agreed. Claims 27 and 28 are amended accordingly, although applicants do not acquiesce to the grounds of rejection.

The remaining issue in this case is the rejection under 35 U.S.C. § 103 over Sullivan *et al.* in view of Coulter *et al.* and Smith *et al.* In the response filed on January 17, 1995, applicants argued that one of ordinary skill in the art could not have predicted that F(ab) fragments would be useful for treating snake envenomation. Briefly, applicants argued that,

(1) clearance of digoxin (taught by Smith) using F(ab) fragments was not dispositive because F(ab)-digoxin complexes differ from F(ab)-venom complexes in both size and rate of clearance from the body (Response at pages 4-5), and it was very predictable that F(ab)'s would have a highly probable chance of success against digoxin;

(2) F(ab) fragments differ from $F(ab)_2$ fragments in size, number of binding sites, and ability to cross-link after binding to antigen (Response at pages 6-7);

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(3) F(ab) to the toxin α-amanitin greatly increased the toxicity of the α-amanitin in mice (Response at page 7); and

(4) in 1994, others of skill in the art continued to recognize that redistribution of systemic toxicity (as occurred with α-amanitin F(ab)) is a potential outcome of immunotherapy (Response at pages 7-8).

Applicants submit that these arguments alone were enough to rebut a *prima facie* case of obviousness (which applicants do not suggest exists here). However, the Examiner did not allow the claims at that stage. Applicants believe that under the standards for overcoming an obviousness rejection, the claims are allowable.

The Court of Appeals for the Federal Circuit recently addressed a similar situation in In re Soni, 34 U.S.P.Q.2d 1684 (Fed. Cir. 1995). In Soni, Appellants claimed a composition comprising in part an organic polymer having a molecular weight greater than 150,000. The specification stated that the compositions of the invention exhibited "unexpectedly improved physical and electrical properties compared to lower molecular weight compositions." Id. at 1687. The specification contained data to support the improved properties. Id. at 1686-1687. Soni argued that the data successfully rebutted the *prima facie* case of obviousness.

The Board upheld the rejection and stated that Soni's claim that the results were unexpected was not supported by factual evidence. The Court disagreed with this requirement and reversed the rejection. First, the Court cited case law stating that a

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prima facie case of obviousness can be rebutted with a showing of unexpected results. Id. at 1687. The unexpected results must be established by factual evidence, not simply by argument or conclusory statements. Id.

The Court pointed out that Soni's specification contained specific data indicating improved properties. Soni further stated that the results were unexpected. Id. at 1688. The Court held that a statement that the results were unexpected "should suffice to establish expected results in *the absence of evidence* to the contrary." Id. at 1688, emphasis in original.

The Soni decision is relevant to this case. Applicants submit that the arguments and cited references discussed in the Response of January 17, 1995 successfully rebutted the obviousness rejection. However, as further support, applicants submitted a declaration of Dr. Damon Smith, an expert in the field of immunotherapy. The declaration is Exhibit 2 of the January 17, 1995 response.

The data presented in Exhibit 2 show that the F(ab) antivenins of the invention are much more potent than conventional antivenin, and can be administered in lower dosages. In addition, no allergic events were observed following F(ab) treatment. The data establish substantially improved results. The statements in the response filed on January 17, 1995 clearly establish the unexpected nature of the results. These statements are not conclusory - they are supported by scientific data and by the known chemical properties of F(ab).

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In the Advisory Action dated February 9, 1995, the Examiner did not address applicants' arguments. Instead, he took issue with several points in Dr. Smith's declaration. To address these issues and to clarify the state of the art at the time the invention was made, applicants requested a personal interview with the Examiner, who kindly agreed. The interview was held on May 25, 1995, with Examiner Schwadron, inventor John Sullivan, and applicants' representatives, Tom Jenkins and Jane Potter, in attendance. Applicants believe that the interview helped to clarify the issues and sincerely appreciate the Examiner's comments and questions.

After the interview the Examiner stated that it would be helpful to receive a declaration from Dr. Sullivan. The declaration would summarize Dr. Sullivan's conclusion, based on discussions with, and beliefs and knowledge at that time by others of skill in the art, that F(ab) would not be expected to successfully neutralize snake venom *in vivo*, reversing clinical toxicity. The Examiner also gave weight to Dr. Sullivan's argument that based on the structure of IgG(T), one of ordinary skill in the art would expect $F(ab)_2$ to be a better antivenin than F(ab).

Dr. Sullivan's declaration is attached as Exhibit 1. Dr. Sullivan explains that he and his colleagues did not expect F(ab) to work as antivenin. Decl. at ¶ 5. Dr. Sullivan also explains in detail why one of ordinary skill in the art would expect $F(ab)_2$ to be more effective than F(ab), based on the earlier work with IgG(T). Decl. at ¶ 6.

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Applicants submit that Dr. Sullivan's declaration adequately addresses the Examiner's concerns about the improved results and the unexpected nature of the improvement. Applicants submit that the rejection should be withdrawn on the basis of the previous record in this case, with further support and confirmation by Dr. Sullivan in his declaration.

As even more recent evidence of the non-obviousness of applicants' invention, applicants submit herewith an abstract of Sorkine, M. *et al.*, "Comparison of $F(ab)'_2$ and Fab efficiency on plasma extravasation induced by *Viper aspis* venom," Toxicon 33:257 (1995) (Exhibit 2). Applicants provided the Examiner with a copy of the abstract prior to the interview, and at the interview the Examiner stated that the abstract may support the non-obviousness of the invention.

Sorkine *et al.* compared, in a mouse model, the effect of $F(ab)'_2$ and Fab on capillary permeability increase induced by *Vipera aspis aspis* venom. Edema is a major factor of envenomation, and reversal of the edema is important in treatment. The abstract reports that, (1) F(ab) was five times more effective than $F(ab)'_2$; and (2) F(ab) injected after $F(ab)'_2$ had a residual effect, whereas immunoglobulins injected after $F(ab)'_2$ had no effect.

The abstract reaches two conclusions that are entirely consistent with Dr. Sullivan's declaration and with applicants' previous arguments. First, the abstract states that "the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." This supports the

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unpredictability in this art. Second, Sorkine *et al.* conclude that F(ab) may be more effective at reducing venom-induced capillary permeability increase because "[t]he smaller size of Fab results in faster diffusion and a greater volume of distribution." (Abstract, last two lines.)

Applicants have informed the undersigned that the ovine F(ab) used by Sorkine *et al.* in this study was produced by the assignee of the present application, Therapeutics Antibodies, Inc. The abstract states that no difference was observed in the efficiency of ovine and equine F(ab). Thus, as pointed out in the abstract, the effectiveness of the F(ab) can be attributed to its size, and is not specific to one preparation of F(ab).

Sorkine *et al.* pointed out that the ability of immunoglobulin fragments to neutralize venom *in vitro* does not reflect their *in vivo* efficiency. A separate group of workers in this field recently reached a similar conclusion about the lack of predictability in this area. Laing, G.D. *et al.*, "Experimental assessment of a new, low-cost antivenom for treatment of Carpet Viper *(Echis ocellatus)* envenoming," Toxicon 53:307-313 (1995) (Exhibit 3), found that an ovine F(ab) preparation provided the best protection in rats, compared with three $F(ab)'_2$ antivenom preparations.

The authors described the advantages of F(ab). First, F(ab) is univalent and does not cross-link antigen, unlike $F(ab)'_2$. This helps to decrease the side effects of immunotherapy. (Page 311, second full paragraph.) Second, "the potency assays

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indicate the superiority of the Fab monospecific Echis antivenom in all respects." (Page 312, first full paragraph.)

However, the authors caution that "the findings may or may not correlate with the clinical observations and may not be infallible predictors of clinical efficacy." Furthermore, "[t]he only truly realistic assessment of such antivenoms, however, is to perform a properly controlled clinical comparative trial . . ." (Page 312.)

These conclusions are highly relevant to the present application. The Examiner maintains that the claimed F(ab) antivenom is obvious over anti-digoxin F(ab) and whole IgG antitoxin - this allegedly was true at the time the application was filed, in 1984. However, more than ten years later, persons of skill in this art state that tests of antivenom F(ab) in animals may not correlate with clinical efficacy (Laing *et al.*, 1995). Furthermore, in 1994, Sorkine *et al.*, also of skill in this art, stated that "*in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency." (Exhibit 2.)

Thus, use of F(ab) fragments to treat envenomation continues to be an unpredictable art: it was unpredictable in 1984, as Dr. Sullivan states in his declaration, and it is unpredictable today, as described by Sorkine *et al.* and Laing *et al.* Applicants submit that the data and statements in Exhibits 1-3 are yet further support for the previous record in this case, which establishes the non-obviousness of the claimed invention. Applicants respectfully request that the Examiner withdraw the

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rejection and allow the claims to issue. As Dr. Sullivan stated at the interview, the clinical trials are very positive, and physicians are waiting for this product, which clearly is a patentable advance over the prior art. As an example, he recently was consulted on a 72 year old man in South Carolina who received a life-threatening snake bite. The patient was allergic to current Wyeth antivenin and had a life-threatening reaction on treatment. Dr. Sullivan is convinced that the F(ab) fragment would have been safe and efficacious in treating this man, but it was not available, even for compassionate use.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request the timely allowance of the pending claims.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 06-0916. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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By: _____
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Dated: October 5, 1995

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